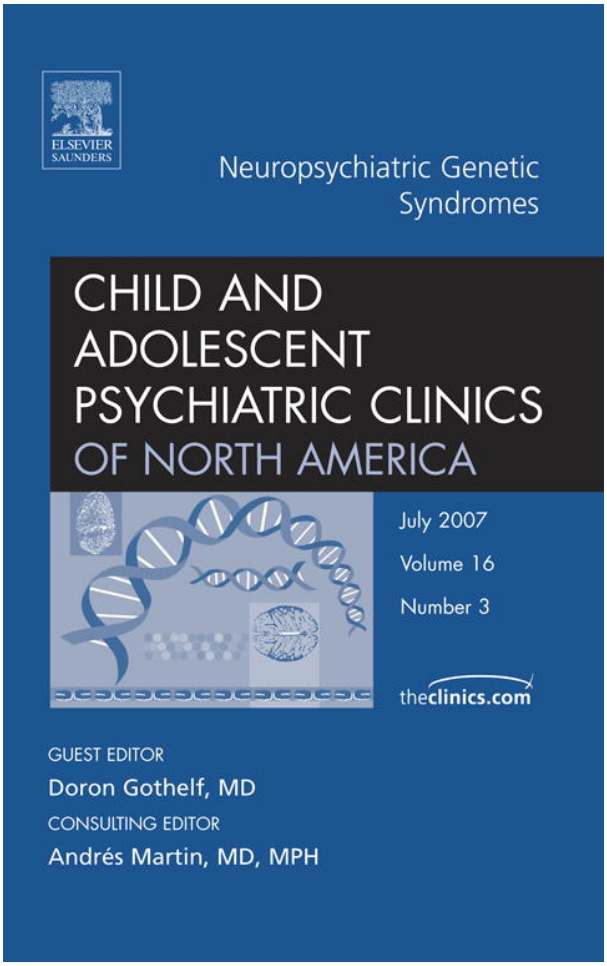

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Imaging Genetics for Neuropsychiatric Disorders

Andreas Meyer-Lindenberg, MD, PhD, MSc[a,b,c,*],
Caroline F. Zink, PhD[a,c]

[a]*Unit for Systems Neuroscience in Psychiatry, 9000 Rockville Pike, Building 10/Room 3C101, Bethesda, MD 20892, USA*
[b]*Neuroimaging Core Facility, 9000 Rockville Pike, Building 10/Room 3C101, Bethesda, MD 20892, USA*
[c]*Clinical Brain Disorders Branch; Genes, Cognition and Psychosis Program, National Institute of Mental Health, NIH, DHHS, 10-3C103, 9000 Rockville Pike, Bethesda, MD 20892-1365, USA*

The biological complexity of psychiatric genetics is daunting. It is true that for many important illnesses in this area, such as autism, schizophrenia, and anxiety disorders, the heritability is considerable. Unfortunately, however, that does not imply that the genes associated with these disorders are easy to find or characterize. It is clear that psychiatric illnesses are genetically complex in the sense that they are not caused by single genetic mutations of large effect [1]. Instead, multiple genetic variants come together, likely in interaction with each other and with the environment to increase or decrease an individual's susceptibility for these disorders, which may then lead to illness if the relationship of genetic predisposition and environmental and individual stressors is unfavorable. It is still debated how many genes contribute to each of these disorders [2].

Some researchers in psychiatric genetics believe that a handful of common genetic variants, each by itself increasing risk by only a small amount, is the most likely model (the so-called "common disease–common variant hypothesis") [3], whereas others believe that much larger numbers of diverse mutations of higher risk will be found [4]. Either way, identification of genes in this setting by classical linkage approaches is not easy. Such a difficulty in psychiatric genetics is shared with many other common and complex disorders (eg, hypertension and diabetes). A second level of complexity is unique to neuropsychiatry, however [5]: genetic variants that result in molecular

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* Corresponding author.
E-mail address: andreasm@mail.nih.gov (A. Meyer-Lindenberg).

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changes whose functional impact can only be understood if considered in terms of the effect on arguably the most complex entity known, the human brain. Understanding this process is made even more difficult by the fact that our knowledge about the underlying neurobiology of most of the clinical symptoms is sparse. For example, there is, as yet, no consensus on what underlies delusions or social dysfunction.

One approach that has proven useful in this difficult-to-negotiate terrain is imaging genetics [5]. The power of neuroimaging to characterize various aspects of brain structure and function in vivo is combined with genetic data to link interindividual variation in imaging parameters to genetic variants that these individuals carry. If the genetic variants under study have been associated with neuropsychiatric, behavioral, or cognitive phenotypes, then the identification of neural systems linked to these variants implicates these systems in mediating genetic risk for the disorders to which the genetic variants have been linked. This imaging genetics approach benefits from the fact that genes are likely to have a bigger effect on the level of biologic processing than on emergent mental or social and behavioral phenomena. In other words, the penetrance is likely to be higher on the neural systems level. In this way, imaging genetics leverages the genetic information usually obtained in large-scale association studies to discover neural systems important in heritable psychiatric disorders [5].

Imaging genetics is, at least in current usage, not primarily an approach to find genes but rather a method to identify brain mechanisms to which genes are linked—a ''reverse genetics'' approach. Precisely because the genetic risk architecture of neuropsychiatric disorders is complex and each individual genetic variant is likely to only contribute a minor fraction to disease risk, it becomes possible to study the impact of genetic variations on the brain in samples of healthy humans. Such healthy samples are much easier to acquire than samples of patient populations and are free of various disease-related confounds that are difficult to control.

In this article, we focus on two applications of this methodology of relevance for child and adolescent psychiatry. First, we present work dissecting a unique neuropsychiatric disorder already manifest in early childhood, Williams syndrome (WS). Research in this area shows unambiguously that imaging genetics can define dissociable neural systems underlying complex behavioral and cognitive phenotypes of genetic origin in WS [6]. Second, we move from this work in patients to discuss studies of genetic risk variants for depression and violence in large samples of healthy human participants, which begins to delineate neural circuitry for a mechanism of critical importance in psychiatric genetics, namely gene-by-environment interactions [7].

Williams syndrome: a unique neuropsychiatric disorder

A fascinating condition that provides a solid starting point for imaging genetics is WS, a neurodevelopmental disorder that presents a unique

combination of neuropsychiatric symptoms in the context of a known genetic mechanism (Fig. 1). Unequal homologous recombination at flanking repeats during meiosis [8] leads to a hemizygous deletion (see Fig. 1B) of approximately 1.6 megabases (see Fig. 1C), containing approximately 25 genes, on chromosome 7q11.23. The occurrence of WS is infrequent but may not be as rare as once thought, with new prevalence estimates as high as 1:7500 [9].

WS encompasses various somatic abnormalities, especially in the cardiovascular system, but also in the endocrine, orthopaedic, and gastrointestinal systems, and abnormal facial features (see Fig. 1A) [10]. Many of these symptoms are caused by haploinsufficiency for the *elastin* gene (*ELN*), which leads to connective tissue abnormalities and many of the facial features [11]. Neural involvement is indicated by symptoms such as

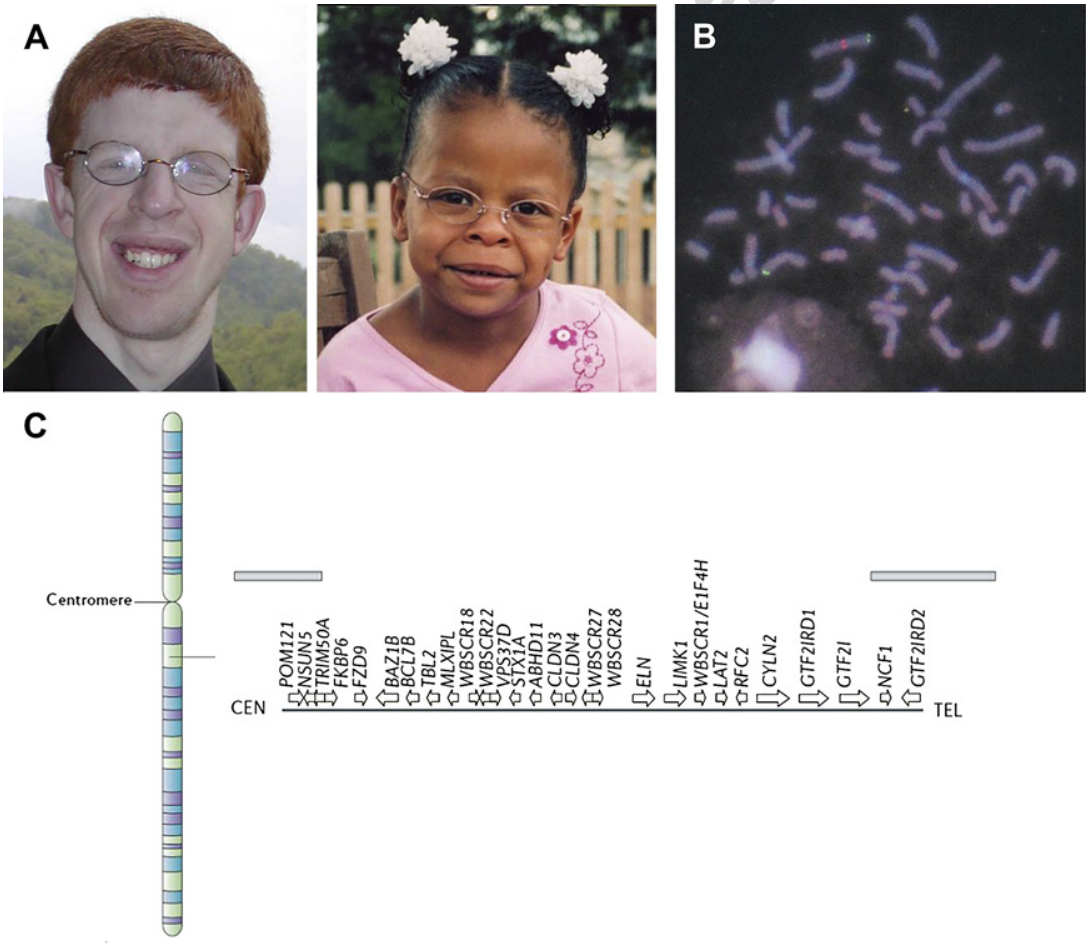

Fig. 1. Williams syndrome. (*A*) Typical WS facial features. (*Courtesy of* Williams Syndrome Association, Clawson, MI; with permission.) (*B*) Chromosomal display during mitosis showing (*in green*) a probe in the WS region present in only one chromosome 7, which indicates its absence on the corresponding chromosome hemideletion. (*Courtesy of* Holly H. Hobart, PhD, Las Vegas, NV.) (*C*) Chromosomal location of the hemideleted region. (*From* Meyer-Lindenberg A, Mervis CB, Berman KF. Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour. Nat Rev Neurosci 2006;7(5):381; with permission.)

hyperreflexia, nystagmus [12], hypersensitivity to sound [10], coordination difficulties, learning difficulties, and mild to moderate mental retardation.

Although many neurodevelopmental disorders impact on multiple somatic and neural systems, a key feature of WS that has attracted considerable attention is its distinctive cognitive profile with a severe visuospatial constructive deficit, combined with relative strengths in verbal short-term memory and language. There is also a pronounced problem with long-term memory. Besides the cognitive symptoms, the second striking neuropsychiatric feature involves high sociability [13,14], social fearlessness, and empathy [14]. Remarkably, this feature goes along with increased anxiety related to nonsocial circumstances, for example phobias. Multimodal neuroimaging allows the delineation of structural and functional alterations in participants with WS compared with normal controls. Although the impact of the condition on IQ usually results in a difference in intelligence and ability to participate in imaging studies between healthy participants and persons with WS, this can be avoided by studying selected subgroups of people with WS and normal intelligence [6].

Structural imaging in Williams syndrome

Structurally, the brain size of people who have WS is reduced [15], particularly in the parietal lobule [16], whereas cerebellar size is preserved [17,18]. These volume changes can be further localized by methods such as voxel-based morphometry, which allows for the mapping of volume changes unconstrained by anatomic landmarks. In our own work, this voxel-based morphometry approach identified circumscribed symmetrical gray matter volume reductions in WS in three regions (Fig. 2A): (1) intraparietal sulcus, (2) around the third ventricle, and (3) orbitofrontal cortex [19]. The intraparietal sulcus finding was recently confirmed in typically functioning children who have WS [20] and was again found together with abnormalities in the superior parietal lobule [16] in typically functioning individuals who have WS [21]. The latter study also had some discrepant findings, especially in the orbitofrontal cortex, but these findings were caused by the specific methodology applied, and the results are convergent if method-related confounds are adequately considered [22]. These regional volume analyses are extended by analyses of cortical shape, which show abnormally increased gyrification in the parietal and occipital lobes [23] and the temporoparietal zone [24], gyral length reductions [25,26], and convergent evidence for reductions in sulcal depth in the intraparietal sulcus in normal IQ participants who have WS [27] and, together with various other symmetric folding abnormalities, in individuals who have mental retardation [28].

Functional neuroimaging in Williams syndrome

Multimodal neuroimaging approaches have been used to identify functional correlates of the aforementioned structural abnormalities in two

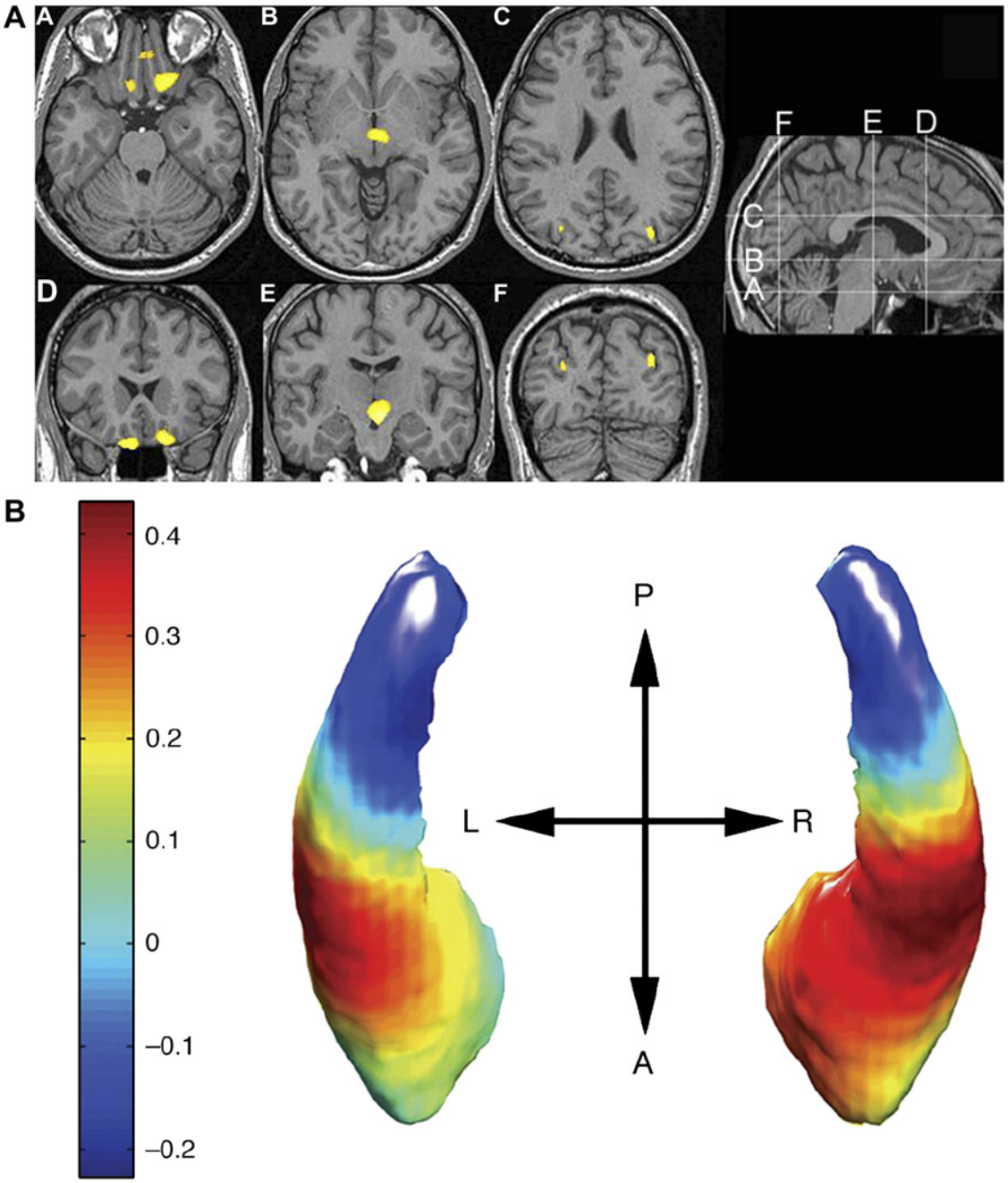

Fig. 2. Structural abnormalities in WS. (*A*) Panel graph shows regional volume reductions in the intraparietal sulcus, hypothalamus, and orbitofrontal cortex of participants with WS compared with normal controls. (*From* Meyer-Lindenberg A, Kohn P, Mervis CB, et al. Neural basis of genetically determined visuospatial construction deficit in Williams syndrome. Neuron 2004;43(5):626; with permission.) (*B*) Map of shape change rendered on an average hippocampal template, posterior view. Negative: relative local volume reduction in WS relative to controls. Positive: relative local volume expansion in WS relative to controls. (*From* Meyer-Lindenberg A, Mervis CB, Sarpal D, et al. Functional, structural, and metabolic abnormalities of the hippocampal formation in Williams syndrome. J Clin Invest 2005;115(7):1889; with permission.)

domains prominently altered in WS: visuoconstruction and social cognition. Disrupted visuospatial construction, ''the ability to visualize an object (or picture) as a set of parts and construct a replica of the object from those parts'' [29], is a neuropsychological hallmark of WS [30]. Visual processing in human and nonhuman primates is organized into two functionally specialized, hierarchically organized processing pathways—a ventral or ''what'' stream for object processing and a dorsal or ''where'' stream for spatial processing [31]. The visuospatial construction disabilities, but relatively good face and object processing skills [32], in WS suggest problems specifically in the dorsal visual processing stream [33–36], with relatively intact ventral stream function (Fig. 3A).

A comprehensive test of the visual processing hierarchy in high-functioning individuals who have WS showed intact ventral stream processing, as measured with functional MRI during passive viewing of pictures, while paying attention to picture identity and during a shape-matching task [19]. In contrast, dorsal stream function was consistently abnormal while participants attended to the spatial locales of the same pictures or performed a two-dimensional puzzle task. Hypofunction was observed immediately adjacent to and anterior to the intraparietal sulcus region in which we had identified decreased gray matter volume and sulcal depth [19,27]. Such results suggested that the structural change may be impeding information flow in the dorsal visual processing stream. We formally tested this hypothesis with path analysis, a method that allows statistical assessment of interactions among regional nodes in a predefined neural system model, which we based on previous path analyses of the visual system. Upon comparison, the only significant difference between the WS group and normal controls was the absence of a path from the structurally abnormal region into lateral (parietal) dorsal stream, which confirmed the hypothesis that this region might be a roadblock that impedes efficient dorsal stream processing in WS.

Functional correlates of the orbitofrontal cortex structural abnormality in WS came into focus in an examination of fear processing related to social cognition. We performed an experiment to study fear-related circuitry [37], with tasks presenting threatening visual stimuli [38] divided into two sets: (1) fearful scenes, which are rarely encountered and socially less relevant, and (2) angry and fearful facial expressions, which are commonly encountered and socially highly relevant. We first focused on amygdala, which is critical for basic emotional—especially fear—processing [39]. The lateral nucleus of the amygdala receives and integrates sensory and prefrontal/limbic inputs and then excites, possibly indirectly, neurons in the central nucleus that evoke fear responses via their projections to brain stem regions, including periaqueductal gray and reticular formation [39]. Amygdala reactivity in WS to threatening socially relevant stimuli was significantly diminished (Fig. 3B) [40], which corresponded to the diminished fear of strangers and consequent social disinhibition [14]. Conversely and again in excellent agreement with the clinical profile of WS, amygdala reactivity abnormally

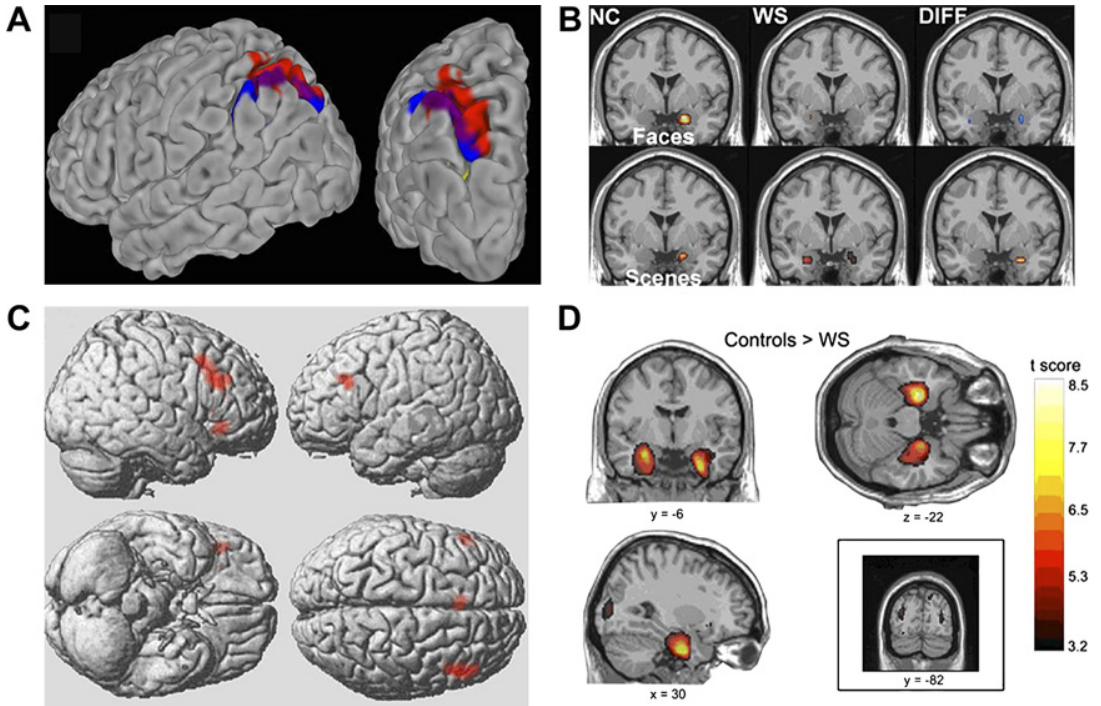

Fig. 3. Functional abnormalities in WS. (*A*) Hypoactivation during various visuospatial tasks (*red, blue, purple*), found directly adjacent to area of structural change in the intraparietal sulcus (*yellow*). (*From* Meyer-Lindenberg A, Kohn P, Mervis CB, et al. Neural basis of genetically determined visuospatial construction deficit in Williams syndrome. Neuron 2004;43(5):627; with permission.) (*B*) Amygdala activation ($P < .05$), corrected for multiple comparisons in amygdala for face (*top row*) and scene (*bottom row*) stimuli, rendered on normal coronal MRI at $\pm$ 1 mm to the anterior commissure in neurologic orientation (ie, left+left). First column: normal controls (NC). Second column: participants with WS (WS). Third column: significant differences (DIFF) between groups (blue NC > WS, red WS > NC). (*From* Meyer-Lindenberg A, Hariri AR, Munoz KE, et al. Neural correlates of genetically abnormal social cognition in Williams syndrome. Nat Neurosci 2005;8(8):991; with permission.) (*C*) Regions of significant group difference in cortical reactivity to the faces versus the scenes matching task, rendered in red on standard brain surface. Statistical threshold is $P < .05$, corrected for multiple comparisons. (*From* Meyer-Lindenberg A, Hariri AR, Munoz KE, et al. Neural correlates of genetically abnormal social cognition in Williams syndrome. Nat Neurosci 2005;8(8):992; with permission.) (*D*) Marked reduction of regional cerebral blood flow (measured using positron emission tomography) in the anterior hippocampal formation bilaterally in participants with WS relative to normal controls ($P < .05$), corrected for multiple comparisons. Inset shows reduction in rCBF in the intraparietal/occipitoparietal sulcus in WS ($P < .001$), uncorrected. (*From* Meyer-Lindenberg A, Mervis CB, Sarpal D, et al. Functional, structural, and metabolic abnormalities of the hippocampal formation in Williams syndrome. J Clin Invest 2005;115(7):1890; with permission.)

increased to socially irrelevant stimuli, which offered a potential mechanism for the high rate of nonsocial anxiety in WS [41]. The same study uncovered differences in prefrontal cortical structures regulating the amygdala. Healthy controls differentially activated dorsolateral-prefrontal, medial-prefrontal, and orbitofrontal cortex (OFC), whereas high-functioning participants with WS did not (Fig. 3C). In particular, the OFC did not show any activation versus the control condition in the WS group. Taken together with the structural abnormality in the OFC, this provided convergent evidence for

a deficiency of the OFC in the context of social processing. Lesions of OFC are associated with social disinhibition [42]. OFC and OFC-amygdala interactions are critical for stimulus-reinforcement association learning, and in social cognition the role of OFC-amygdala interactions has been hypothesized to link sensory representations of stimuli with the social judgments we make about them on the basis of their motivational value [43]. The disruption of OFC-amygdala circuitry was further substantiated by an analysis of functional interactions between prefrontal cortex and amygdala, which showed that OFC did not interact with amygdala in WS, whereas a significant negative correlation was found in controls. Such a result suggested a primary OFC deficiency that would be predicted to contribute to social disinhibition, reduced reactivity to social cues, and increased tendency to approach strangers, as is typical for individuals who have WS. In contrast, a negative interaction between amygdala and medial prefrontal cortex (perigenual cingulate) was found in healthy controls and subjects who have WS, in whom it was even facilitated by dorsolateral-prefrontal cortex. An important role for this cingulate-amygdala circuit emerged in our further studies that examined genetic variants linked to depression and violence (see later discussion).

We also performed a multimodal study of the hippocampal formation [44], because several cognitive domains that are linked to it are severely affected in WS, including spatial navigation [45,46] and verbal [47] and spatial [48] long-term memory. Structural imaging findings in the hippocampal formation were subtle and restricted to shape changes (Fig. 2B), but functional abnormalities were profound. Baseline blood flow, measured with oxygen-15 water positron emission tomography, was strongly reduced bilaterally in the hippocampal formation, extending into the entorhinal cortex (Fig. 3D). We also used proton magnetic resonance spectroscopy for an in vivo assay of N-acetyl aspartate, a cellular integrity marker and measure of synaptic abundance produced primarily in neurons and related to mitochondrial oxidative phosphorylation [49]. Reduced N-acetyl aspartate (as a ratio to creatine), more pronounced on the left, was found in participants who have WS, which indicated overall depression of hippocampal energy metabolism and synaptic activity in WS. During a functional MRI study of passive viewing of face and house stimuli, no activation was seen in the anterior hippocampal formation in an anatomic locale that corresponds well with the resting positron emission tomography blood-flow reduction, which demonstrated that the hippocampal formation exhibited processing abnormalities under stimulation and changes in resting blood flow and metabolism that might underlie the hippocampal formation–dependent cognitive abnormalities in WS.

Regulatory limbic interactions in depression and gene-by-environment interactions

Multimodal neuroimaging delineated dissociable systems impacted by genetic haploinsufficiency in WS that provided neural mechanisms for the

complex neuropsychiatric phenotype in this syndrome. Although in WS the genetic "lesion" is well known and characterized, the phenotype associated with most genetic risk variants in psychiatry is usually only obvious in group comparisons and not on the level of individual subjects. The precise functional impact of variants on gene function is often difficult to quantify, especially for noncoding polymorphisms. Considerable advances have been made in identifying those variants, and imaging genetics has been helpful in defining the associated neural mechanisms. We focus on the aforementioned cingulate-amygdala circuit, which is involved in amygdala regulation, emotional control, and social behavior, because it has emerged as a potential mechanism underlying one of the most important phenomena in psychiatric genetics: gene-by-environment interactions [7].

Clinical experience and patient self-report often suggest a role for environmental adversity in the precipitation of psychiatric episode (eg, depression). Groundbreaking recent epidemiologic evidence has directly demonstrated gene-by-environment interactions for specific susceptibility gene variants linked to serotonergic neurotransmission, SLC6A4 [50], and a variable number of tandem repeats polymorphism in MAO-A (Fig. 4) [51,52]. Because both of these genes impact on the serotonin system, it seems reasonable to expect that studies of neural systems especially responsive to serotonin could be associated with gene-by-environment interactions. In humans, the subgenual cingulate (BA25) displays the highest density of 5-HTT terminals within the human cortex [53] and is impacted by serotonin reuptake inhibitor antidepressants [54]. Even transient alterations in 5-HT homeostasis during early development modify neural connections implicated in mood disorders and cause permanent elevations in anxiety-related behaviors during adulthood [55].

The serotonergic system has been implicated in impulsivity and violent behavior in animals and humans [56]. The subgenual cingulate [57–59] receives strong afferent input from the amygdala and is reciprocally connected to more dorsal parts of the cingulate, which project back to amygdala [60]. Importantly, convergent evidence strongly suggests that amygdala-cingulate interactions represent a functional feedback circuitry regulating amygdala processing of environmental adversity; stimulation of perilimbic prefrontal cortex inhibits amygdala [61], and lesions of this region markedly impair fear extinction [62]. Extinction is the active process by which previously acquired responses to a conditional stimulus are lost if this stimulus is no longer followed by the unconditional stimulus. Because such responses are likely to have arisen through adverse environmental circumstances (eg, a fear response to caregivers after experiencing abuse), neural mechanisms that determine the persistence—or otherwise—of conditioned fear are intriguing candidate mechanisms for gene-by-environment interactions. Specifically, given the hypothesis that the amygdala-cingulate circuit is essential for extinction, serotonergic genetic risk variants acting on this circuit may exhibit gene-by-environment interactions because of abnormal interactions in this regulatory circuitry, impairing the capacity to process

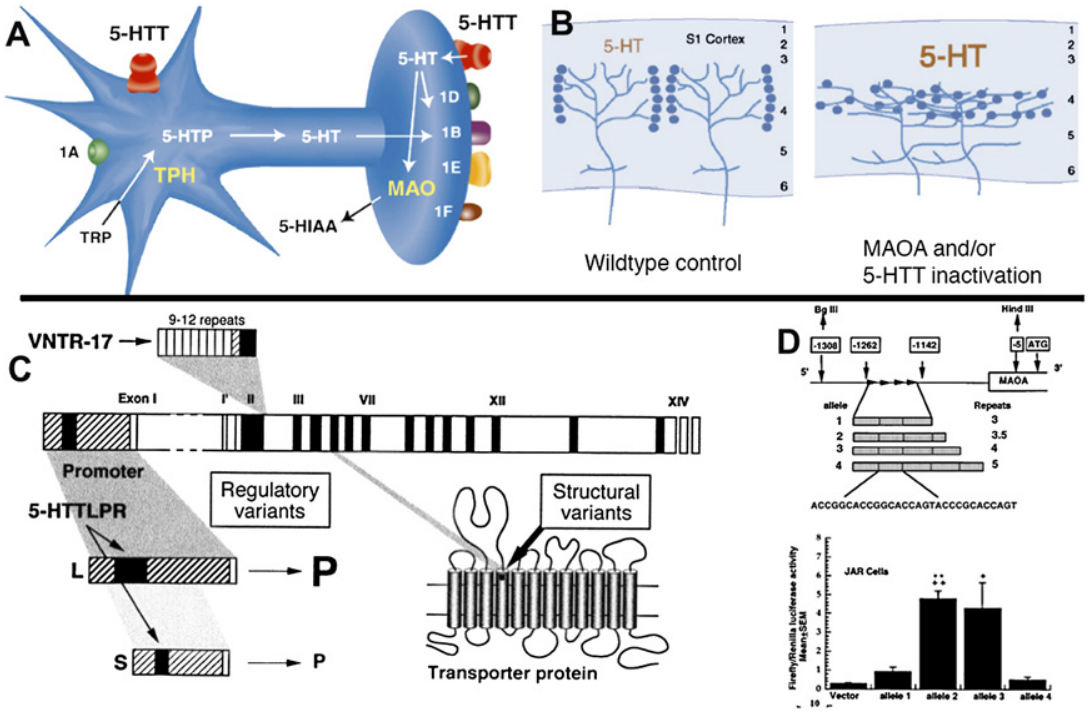

Fig. 4. Serotonergic neurotransmission and associated genetic variants. (*A*) Schematic drawing of serotonergic neuron shows termination of serotonin (5-HT) action by the serotonin transporter (5-HTT) and catabolism by MAO to 5-HIAA and synthesis through tryptophane (TRP) and 5-hyroxytryptophane (5-HTP). Presynaptic serotonin receptors (1A,B,D,E,F) also shown. (*B*) Schematic drawing of neurodevelopmental effects of increased serotonin level caused by inactivation of MAO-A or 5-HTT. (*A, B Adapted from* slide courtesy of K.P. Lesch, MD, Würzburg, Germany.) (*C*) A common variable number of tandem repeat polymorphism in the promoter of the 5-HTT (5-HTTLPR). (*From* Lesch KP, Mossner R. Genetically driven variation in serotonin uptake: is there a link to affective spectrum, neurodevelopmental, and neurodegenerative disorders? Biol Psychiatry 1998;44(3):181; with permission.) Long (L) and short (S) regulatory variants are distinguished, with relatively reduced transcription and activity of the transporter in the S form. (*D*) A common variable number of tandem repeat polymorphism in the promoter of the X-linked MAO-A gene affects transcription, with an optimum range (MAOA-H) of 3.5 or 4 repeats. (*From* Sabol SZ, Hu S, Hamer D. A functional polymorphism in the monoamine oxidase A gene promoter. Hum Genet 1998;103(3):275, 277; with permission.)

contingent negative emotion associations that are bound to arise in the setting of environmental adversity.

The serotonin transporter gene (*SLC6A4*) (see Fig. 4A, C) contains several functional variants, but the one studied most extensively is a variable number of tandem repeats in the 5' promoter region (5-HTTLPR), which influences transcriptional activity and subsequent availability of the 5-HTT [63], with reduced transcription of the 5-HTTLPR short (S) allele in comparison to the long (L) allele. Lower availability of the 5-HTT is predicted to lead to higher levels of synaptic serotonin. Individuals who carry the S allele tend to have increased anxiety-related temperamental traits [63], which are inconsistently related to risk for depression [64]. This is

one of the serotonergic variants in which interaction with environmental adversity has been demonstrated [50], whereas main effects of genetic variation were small. In contrast to the results of traditional clinical association, which are largely inconsistent and weak, imaging-based phenotyping has provided strong evidence of a mechanism by which variation in *SLC6A4* could increase biologic risk for anxiety and depression.

The amygdala has been implicated as a centerpiece of this genetic effect because several functional MRI studies have found that S allele carriers evince an exaggerated amygdala response compared with L homozygote individuals [65–67]. These findings suggest that amygdala hyperreactivity might be a neural substrate of trait anxiety predisposing to psychiatric disease. Recent research has made progress toward characterizing the neural circuit contributing to this finding. Using voxel-based morphometry, a reduction in gray matter was found in the sub- and perigenual cingulate regions of healthy carriers of the S allele compared with matched LL homozygotes (Fig. 5C) [57,68]. Analyses of functional and structural connectivity confirmed close interactions of this cingulate region with amygdala and suggested a feedback circuit that inhibits amygdala function and may be involved in fear extinction (Fig. 5D) [57]. The S allele was associated with reduced coupling between amygdala and the subgenual cingulate, and the degree of that coupling predicted close to 30% in the variability of trait anxiety in these normal individuals [57]. Taken together, these results suggested that psychiatric risk associated with 5-HTTLPR is mediated by a weakened circuit for extinction of fear, which offers an attractive potential (“endo”) mechanism causally related to amygdala hyperreactivity that, at the same time, provides a neural substrate for the impact of early adversity, which would likely produce the kind of fearful associations that require a functional extinction mechanism to mollify (Fig. 5E). A recent paper by Canli and coworkers [69] directly confirmed for the first time that environmental adversity, stratified by SLC6A4 genotype, impacts on amygdala activation and connectivity. Of interest, another study [67] found increased coupling between more anterior medial prefrontal areas (BA10) and amygdala in S allele carriers, possibly indicating interactions with a brain area implicated in high-order goal maintenance and regulation of the internal milieu [70] that might counteract deficiencies in cingulate-amygdala circuitry. Recent analyses from our laboratory suggested that BA10 may impact on amygdala indirectly though a functional effect on cingulate, a two-layered mechanism that would suggest several levels of hierarchy in amygdala regulation [71].

Convergent evidence for the importance of serotonergic neurotransmission for the amygdala-cingulate circuit comes from studies showing an impact of other functional genetic variants in serotonergic metabolism on amygdala activation and regulation. Two studies have shown that a frequent regulatory variant (G(-844)T) of tyrosine hydroxylase 2 biases the reactivity of the amygdala [72,73]. We recently investigated genetic variation in *MAO-A*, encoding monoamine oxidase A, a key enzyme for the catabolism

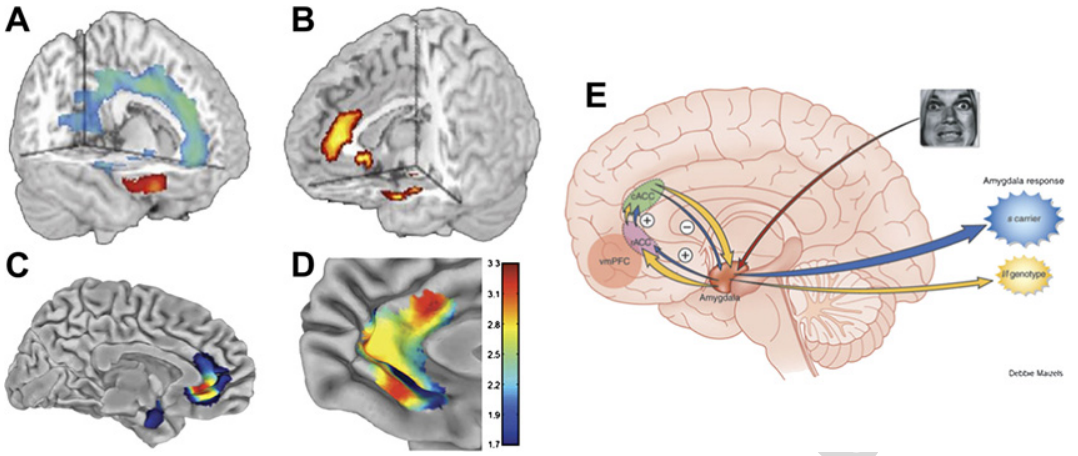

Fig. 5. Neural mechanisms linked to genetic variation in serotonergic risk genes. Structural (using voxel-based morphometry) (*A*) and functional (*Adapted from* Meyer-Lindenberg A, Buckholtz JW, Kolachana B, et al. Neural mechanisms of genetic risk for impulsivity and violence in humans. Proc Natl Acad Sci U S A 2006;103(16):6270; with permission.) (*B*) results (during an emotional faces matching task) show an impact of genetic variation in MAO on amygdala and cingulate volume and function. (*Data from* Meyer-Lindenberg A, Buckholtz JW, Kolachana B, et al. Neural mechanisms of genetic risk for impulsivity and violence in humans. Proc Natl Acad Sci U S A 2006;103(16):6269–74.) Volume is relatively reduced in carriers of the MAOA-L allele implicated in risk for impulsive violence. Amygdala activation is increased, whereas activation of regulatory cingulate regions is decreased. Structural (*C*) and functional (*From* Pezawas L, Meyer-Lindenberg A, Drabant EM, et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci 2005;8(6):829; with permission.) (*D*) connectivity (during a faces matching task) are also affected by genetic variation in 5-HTTLPR (*From* Pezawas L, Meyer-Lindenberg A, Drabant EM, et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci 2005;8(6):830; with permission.) Carriers of the S allele show relative volume reductions in subgenual cingulate and amygdala and reduced connectivity of amygdala to subgenual cingulate. (*E*) Model drawing of a core circuit for amygdala regulation and fear extinction linking amygdala and cingulate and impacted by serotonergic risk genes. (*Adapted from* Hamann S. Blue genes: wiring the brain for depression. Nat Neurosci 2005;8(6):702; with permission.) Reduced connectivity (5-HTTLPR) or cingulate activation (MAO-A) predict amygdala hyperactivation by reduced feedback inhibition as an endomechanism underlying anxiety and impulsivity associations of these genes. An anterior medial prefrontal area might modulate this effect.

of serotonin and other neurotransmitters during neurodevelopment [74]. The human *MAO-A* gene contains a common variable number of tandem repeats polymorphism that again affects transcriptional efficiency; enzyme expression is relatively high for carriers of 3.5 or 4 repeats (MAOA-H) and lower for carriers of 2, 3, or 5 repeats (*MAOA-L*) (see Fig. 4D) [75]. Although inconsistent evidence exists for the association of genotype with trait impulsivity in human cross-sectional studies [76], a clear and pronounced gene by environment interaction was found in a large longitudinal study of children followed for 25 years in which *MAOA-L* (which is associated with higher levels of synaptic serotonin during neurodevelopment) predicted violent offenses in male subjects with adverse early experience (maltreatment) [51]. Similar to those in 5-HTTLPR, our multimodal imaging results indicated

an impact on structure and function of amygdala and perigenual cingulate cortex, which suggested a shared mechanism of emotional regulation under serotonergic control and predicted some overlap in clinical association in risk for depression, as has been observed [74,77]. *MAO-A* showed more extensive effects in structure (Fig. 5A) and activation (Fig. 5B), however, notably affecting more caudal regions of the cingulate associated with cognitive control and orbitofrontal cortex. This may reflect the broader metabolic effect of variation in *MAO-A*, which catabolizes not only serotonin but also other neurotransmitters, notably norepinephrine [56], which is also implicated in limbic system development and emotional experience.

Several additional conclusions emerge from this overview of neural mechanisms related to serotonergic genetic variation. First, it was consistently the variants associated with higher serotonin levels (5-HTTLPR S and MAOA-L) that predicted relatively impaired structure and function. Preclinical data that showed enduring neurodevelopmental abnormalities after transient alterations of serotonin (see Fig. 4B) [55] implicate serotonin signaling in human limbic emotional circuitry development and caution against possible adverse consequences of prenatally increased serotonin levels. That the observed genetic data are likely due to a neurodevelopmental effect and not an acute increase in serotonin during adult life is clear from clinical evidence, which shows that higher levels of serotonin are associated with reduced depression and aggression in adults [78]. Second, multiple serotonergic variants, although they have been predominantly studied for different neuropsychiatric disorders, seem to converge on overlapping neural mechanisms, identifying shared circuitry across conventional diagnostic categories that have implications not only for our understanding of these disorders but also to a more biologically based taxonomy. Finally, one key assumption of the intermediate phenotype concept was clearly confirmed in these studies, namely the hope of increased penetrance on the level of biologic intermediates. Although for all of the genes studied, effect sizes for association with psychiatric disease [51,64,79] and personality traits predisposing to it [80,81] are small and often controversial, the imaging literature is remarkably consistent and provides a degree of biologic validation and mechanistic differentiation unattainable on the level of behavioral association.

Summary

In summary, we have given an overview of contributions of imaging genetics to understanding of the neuropsychiatric phenotypes of relevance to child and adolescent psychiatry, taking WS and genetic risk mechanisms for gene-by-environment interactions as illustrative examples. No attempt has been made to be exhaustive. Important applications of imaging genetics to this area of psychiatry are still only beginning, for example, the examination of genetic variation as it impacts brain maturation across childhood

and adolescence [82] or the systems-level study of molecular mediators for attachment, such as the prosocial neuropeptides, in which genetic variation in their receptors has been associated with autism [83,84]. As more genetic variants are being identified and validated in the upcoming whole genome screens of large patient samples, it is to be expected—and hoped—that imaging genetics will be able to contribute an important piece in translational characterization of these disorders that can be used to identify new treatment targets and monitor their efficacy.

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